NTP
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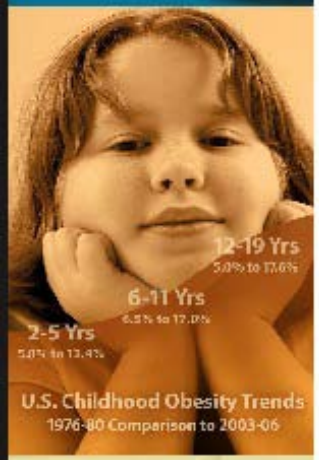

NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

Breakout Group on

Persistent Organic Pollutants (POPs)

Raymond Novak (chair)
Kyla Taylor (rapporteur)

Crabtree Marriott Hotel
January 11-13, 20111

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

POPs Breakout Group Members

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Chad Blystone, NIH/NIEHS/NTP
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*Not able to attend workshop due to weather-related travel delays

Is it possible to identify classes of POPs that should be considered together? If so, which patterns of findings are most consistent? Which are least consistent?

- ~95 separate human studies of varying quality available
- It may be possible with sufficient data mining and analysis to identify classes of POPs that could be considered together in strengthening the finding of an association between exposure and disease (e.g. diabetes).
- Forest plot analysis provides an informative approach for comparing the ORs of individual chemicals either alone or in combination across a battery of studies.

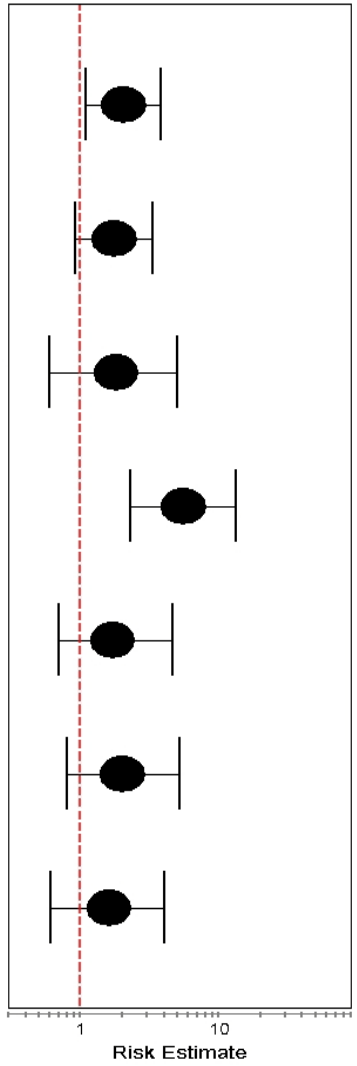
Is it possible to identify classes of POPs that should be considered together? If so, which patterns of findings are most consistent? Which are least consistent? (continued)

- Sufficient evidence of an association with diabetes could be obtained based on forest plot analyses of cross-sectional, prospective/retrospective, and occupational exposure studies
  - Included data from NHANES, maternal, and military Veteran exposure studies
  - Initial data mining indicates strongest correlations for trans-nonachlor, DDE, dioxins/dioxin-like chemicals, including PCBs.
- Insufficient time of analysis of the data during the session to establish whether there is a correlation between exposure to POPs and obesity or metabolic syndrome.
- Further data mining of human and animal studies is required

Prospective studies on PCBs

POPs: Prospective Studies of PCBs or PCB153 with Diabetes

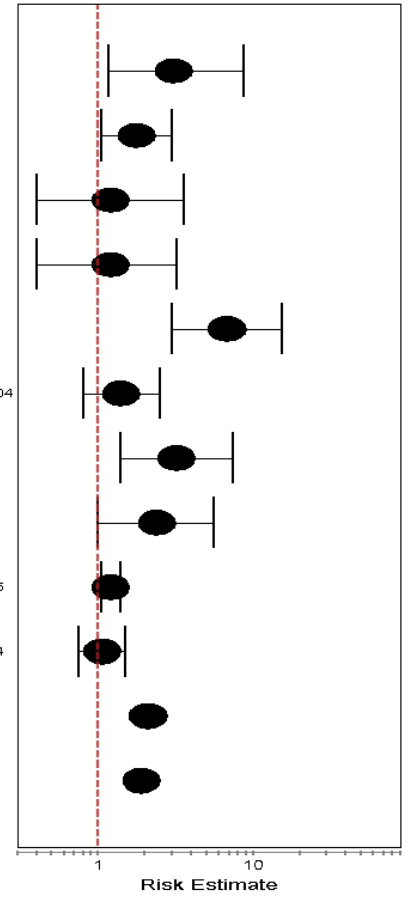
Reference	Study Design	Country and Cohort	N in Analysis (N in Cohort)	Health Outcome	Chemical	Exposure Comparison
Vasiliu, 2006	prospective, IDR	US, MI PBB cohort, women	459 (696)	diabetes (22)	PCBs	5.1-7.0 vs ≤5.0 ppb
Vasiliu, 2006	prospective, IDR	US, MI PBB cohort, men	360 (688)	diabetes (35)	PCBs	>10 vs ≤5.0 ppb
Turyk, 2009a	prospective, RR	US, Great Lakes fish eaters	314 (471)	diabetes, incident (15)	PCBs	4.3-29.8 vs. <1.6 ng/g wet weight, p-trend=0.37
Wang, 2008	nested case control, OR	Taiwan, Yucheng cohort, women	244 (441)	diabetes, T2 (14)	PCBs	121.4 vs. 72.6 ppb, based on chloracne
Wang, 2008	nested case control, OR	Taiwan, Yucheng cohort, men	167 (307)	diabetes, T2 (12)	PCBs	99.4 vs. 53.9 ppb, based on chloracne
Lee, 2010	nested case control, OR	US, CARDIA	95 (180)	diabetes (35)	PCB153	Q2 (205-349) vs. Q1 (≤204) pg/g
Rignell-Hydbom, 2009	nested case control, OR	Sweden, women in WHILA	39 pairs (371)	diabetes	PCB153	>1790 ppt >7 years vs ≤1790 at baseline



Cross-sectional studies on PCBs

POPs: Cross-sectional Studies of PCBs or PCB153 with Diabetes

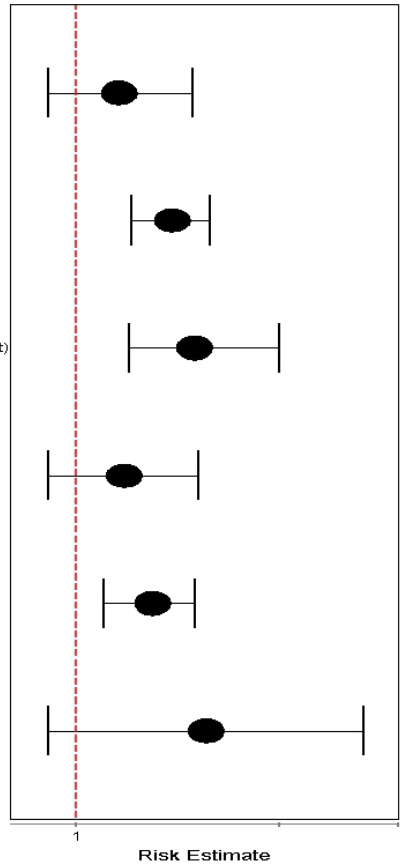
Reference	Study Design	Country and Cohort	N in Analysis (N in Cohort)	Health Outcome	Chemical	Exposure Comparison
Uemura, 2008	cross-sectional, OR	Japan, general pop	1003(1374)	diabetes (14)	PCBs, dioxin-like	≥7.60 to <13 vs. ≤7.60 pg TEQ/g lipid
Ukropec, 2010	cross-sectional, OR	Slovakia, general pop	818 (2047)	diabetes (68)	PCBs	Q4 (1341-2330) vs. Q1 (148-627) ng/g
Jorgensen, 2008	cross-sectional, OR	Greenland, ≥ Inuit parent	692	diabetes (10.3%)	PCBs, dioxin like	Q4 vs Q1, p-trend=0.37
Jorgensen, 2008	cross-sectional, OR	Greenland, ≥ Inuit parent	692	diabetes (10.3%)	PCBs, non-dioxin like	Q4 vs Q1, p-trend=0.42
Lee, 2006	cross-sectional, OR	US, NHANES 99-02	577 (2,106)	diabetes (30)	PCB153	164 ppb vs. ND
Rignell-Hydbom, 2007	cross-sectional, OR	Sweden, fisherman's wives	543	diabetes (7 high)	PCB153	per 100 ng/g ↑ (100ng/g lipid, cases), p-trend=0.004
Codru, 2007	cross-sectional, OR	US, Mohawks near Akwesasne	235 (352)	diabetes	PCBs	756.2 vs 448.6 ppb
Codru, 2007	cross-sectional, OR	US, Mohawks near Akwesasne	235 (352)	diabetes	PCB153	104.4 vs. 59.8 ppb
Rylander, 2005	cross-sectional, OR	Sweden, fishermen	196 (380)	diabetes (6)	PCB153	per 100 ng/g ↑ (560g/g lipid, cases), p-trend=0.005
Rylander, 2005	cross-sectional, OR	Sweden, fishermen's wives	184 (380)	diabetes (7)	PCB153	per 100 ng/g ↑ (230ng/g lipid, cases), p-trend=0.94
Turyk, 2009b	cross-sectional, OR	US, Great Lakes fish eaters	503	diabetes (61)	PCBs, dioxin-like	0.3-1.6 vs <LOD ng/g (p-trend = 0.03)
Turyk, 2009b	cross-sectional, OR	US, Great Lakes fish eaters	503	diabetes (61)	PCBs	3.6-24.4 vs <0.8 ng/g (p-trend = 0.36)



Veteran studies

POPs:Vietnam Veterans with Diabetes

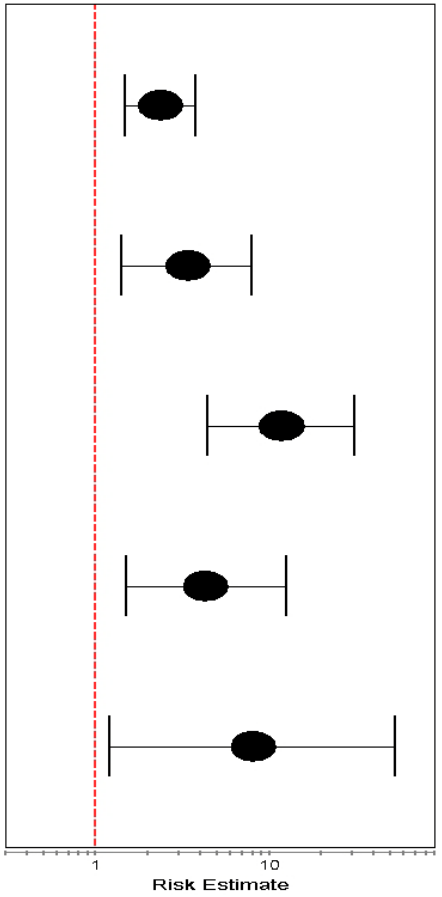
Reference	Study Design	Country and Cohort	N in Analysis (N in Cohort)	Health Outcome	Chemical	Exposure Comparison
Kang, 2006	retrospective, OR	US, Army veterans	2,927	diabetes	Agent Orange	deployed vs non-deployed veterans
Michalek, 2008	retrospective, HR	US, AFHS Op. Ranch Hand	2,469	diabetes (229)	TCDD	Exp.before 1969 and ≥ 90 days spraying
Henriksen, 1997	retrospective, RR	AFHS Op. Ranch Hand	1,559 (2,265)	diabetes (57)	Agent Orange	high (initial>94 ppt) vs current background (≤10 ppt)
Steenland, 2001	retrospective, OR	US, Ranch Hand	990 (1950)	diabetes (147)	TCDD	exposed vs. unexposed, 1980 = 12 ppt
AFHS, 2005	prospective, RR	US, AFHS Op. Ranch Hand	776 (1950)	diabetes (141)	Agent Orange	dioxin adjusted with 2 fold 1987 TCDD, p<0.01
Longnecker, 2000	cross-sectional, OR	AFHS, 1997 exam cycle	299 (1197)	diabetes (61)	TCDD	Q4 (≥5.2 ng/kg lipid) vs. Q1 (<2.8 ng/kg lipid)



Trans-nonachlor

POPs: Trans-nonachlor with Diabetes

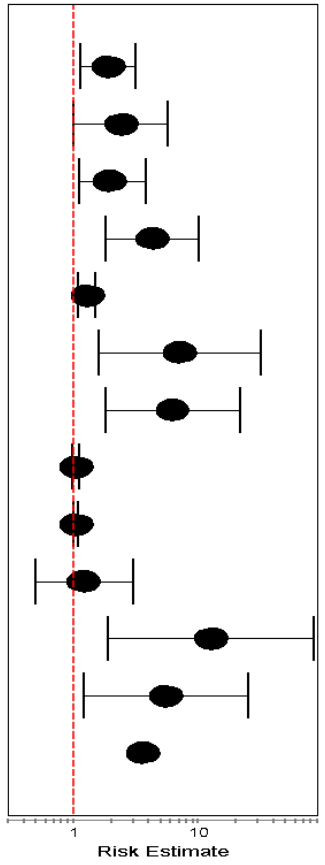
Reference	Study Design	Country and Cohort	N in Analysis (N in Cohort)	Health Outcome	Chemical	Exposure Comparison
Everett, 2010	cross-sectional, OR	US, NHANES 99-04	3,049	diabetes	trans-nonachlor	<14.5 vs ≥14.5 ng/g
Cox, 2007	cross-sectional, OR	US, HHANES 82-84	1308	diabetes (89)	trans-nonachlor	<1.00 vs. >1.80 ppb
Lee, 2006	cross-sectional, OR	US, NHANES 99-02	385 (2,106)	diabetes (54)	trans-nonachlor	114 ng/g vs. ND
Lee, 2010	nested case control, OR	US, CARDIA	85 (180)	diabetes (33)	trans-nonachlor	Q2 (110-174) vs. Q1 (≤109) pg/g *non-linear trend
Son, 2010	cross-sectional, OR	South Korea, Uljin Co.	51 (80)	diabetes (22)	trans-nonachlor	33.1 vs.8.4 ng/g lipid, p-trend=0.02



DDE

POPs: DDE with Diabetes

Reference	Study Design	Country and Cohort	N in Analysis (N in Cohort)	Health Outcome	Chemical	Exposure Comparison
Everett, 2010	cross-sectional, OR	US, NHANES 99-04	3,049	diabetes	p,p'-DDE	<168 vs ≥168.6 ng/g
Cox, 2007	cross-sectional, OR	US, HHANES 82-84	1306	diabetes (89)	p,p'-DDE	<22.81 vs. >58.60 ppb
Ukropec, 2010	cross-sectional, OR	Slovakia, general pop	819 (2047)	diabetes (102)	p,p'-DDE	Q5 (3605-22328) vs. Q1 (54-821) ng/g
Lee, 2006	cross-sectional, OR	US, NHANES 99-02	704 (2,106)	diabetes (53)	DDE	3,700 ng/g vs. ND
Rignell-Hydbom, 2007	cross-sectional, OR	Sweden, fisherman's wives	543	diabetes (8 high)	p,p'-DDE	per 100 ng/g ↑ (240ng/g lipid, cases), p-trend=0.002
Turyk, 2009a	prospective, RR	US, Great Lakes fish eaters	309 (471)	diabetes, incident (22)	DDE	5.4-49.2 vs. <2.2 ng/g wet weight, p-trend=0.008
Codru, 2007	cross-sectional, OR	US, Mohawks near Akwesasne	235 (352)	diabetes	DDE	544.6 vs 246.1
Rylander, 2005	cross-sectional, OR	Sweden, fishermen	196 (380)	diabetes (3)	p,p'-DDE	per 100 ng/g ↑ (1100ng/g lipid, cases), p-trend=0.04
Rylander, 2005	cross-sectional, OR	Sweden, fishermen's wives	184 (380)	diabetes (8)	p,p'-DDE	per 100 ng/g ↑ (990ng/g lipid, cases), p-trend=0.07
Lee, 2010	nested case control, OR	US, CARDIA	86 (180)	diabetes (23)	p,p'-DDE	Q2 (2154-3312 vs. Q1 (≤2153) pg/g
Son, 2010	cross-sectional, OR	South Korea, Uljin Co.	54 (80)	diabetes (25)	p,p'-DDE	667.4 vs. 162.2 ng/g lipid, p-trend<0.01
Rignell-Hydbom, 2009	nested case control, OR	Sweden, women in WHILA	39 pairs (371)	diabetes	p,p'-DDE	>4,600 ppt >7 years vs ≤4,600 at baseline
Turyk, 2009b	cross-sectional, OR	US, Great Lakes fish eaters	503	diabetes (61)	DDE	4.4-24.0 vs <1.2 ng/g (p trend = 0.005)



What are the most useful indicators of exposure and health effect diagnosis?

- Blood and target tissue levels of POPs
- Clinical diagnosis of the disease (e.g. death certificate insufficient for diabetes)

What are the most important factors to include as adjustment variables?

- Age, gender, individual POPs, and exposure to other agents (e.g. pesticides and metals)
- The validity of standardizing/adjusting for blood lipids is unclear
- Adjusting for BMI is controversial (e.g. waist circumference vs. MRI adiposity)
- Measures of health status (e.g. recent weight changes)

Identify major areas of complexity and uncertainty

- The progressive development of disease over time, genetics, age, window of exposure, and lifestyle
- Non-monotonic relationships
- Mixtures of POPs and other environmental chemicals
- Influence of subclinical disease on biomarkers of exposure
- Concurrent medication (e.g. statins, metformin)

In cases where there is a consistent association, does it demonstrate “causality”? If not, how far short is the current literature from demonstrating causality?

- The human data examined are insufficient to establish causality
- There are very strong correlations among some POPs (0.50-0.90) making it difficult to identify individual POPs as potential causal agents
- Mechanistic studies are required to advance our understanding of the role of POPs in metabolic disease development

In cases where there is a consistent association, does it demonstrate “causality”? If not, how far short is the current literature from demonstrating causality? (continued)

- Only when human data are in concurrence with mechanistic studies can we establish causality.
- Such studies should consider factors such as:
  - Windows of exposure
  - Exposure measurements (e.g. the chemical analysis of individual POPs)
  - Mixtures in populations, tissue targets, pathways, and physiological variables (e.g. brown fat, adipose tissue, inflammation)
  - Secondary effects (e.g. hormone production)

Research Strategies and Critical Data Needs: Major Recommendations

- Longitudinal studies of developmental exposures and obesity, diabetes, and related metabolic disturbances
- Studies on age, period, and cohort effects of POPs exposure and incident diabetes
- Meta-analysis of existing studies using individual-level data
- Improve analytical measures to measure low blood volumes and high throughput at a reasonable cost
- Better animal models of diabetes and obesity
- High throughput surrogate exposure measures based on biological activity

Research Strategies and Critical Data Needs: Strategies

- After improving analytical measures use existing longitudinal studies with bio-banked blood
- Identify pathways related to diabetes and related disease states, screen existing POPs for activity in these pathways
- Promote collaboration between epidemiologists, clinicians, and laboratory scientists to work in a true translational way

Research Strategies and Critical Data Needs: Key Data Gaps

- Risk estimates for diabetes and obesity related outcomes
  - Regression coefficients between the POPs and different measurements associated with metabolic syndrome
  - Include glucose levels, lipid profiles, insulin resistance, waist circumference, and blood pressure
- Relationships between Type 1 diabetes and POPs (only one prospective study)
- Type 2 diabetes independent of BMI (thin diabetics representing some 15% of those with T2D)

Research Strategies and Critical Data Needs: Key Data Gaps (continued)

- Interaction between POP exposure and genotype concerning future diabetes (e.g. T1D; T2D) development
- Repeated measurements of exposures and outcomes to follow progression of disease
- Focus on which chemicals are present in the population now and which will continue to increase
  - Generational exposure differences